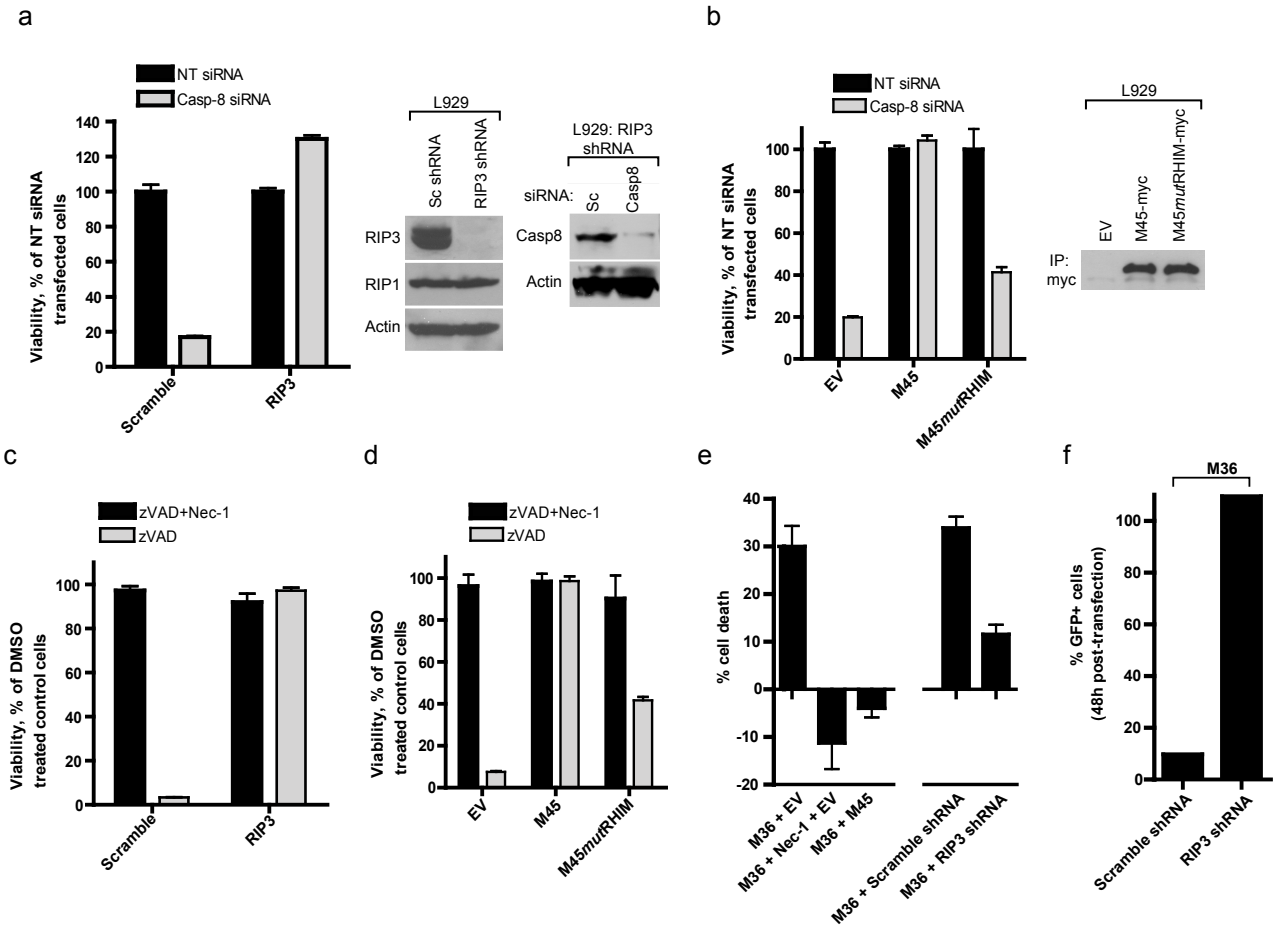
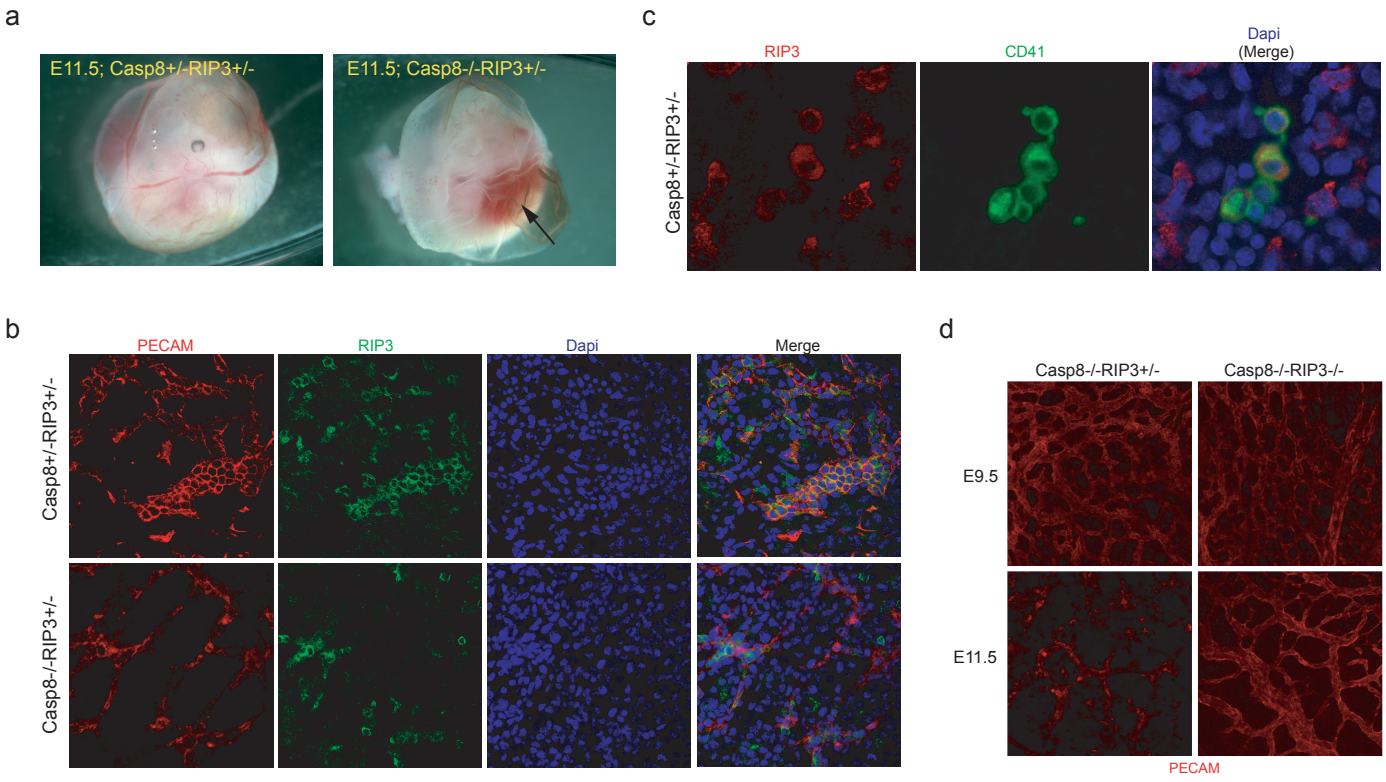
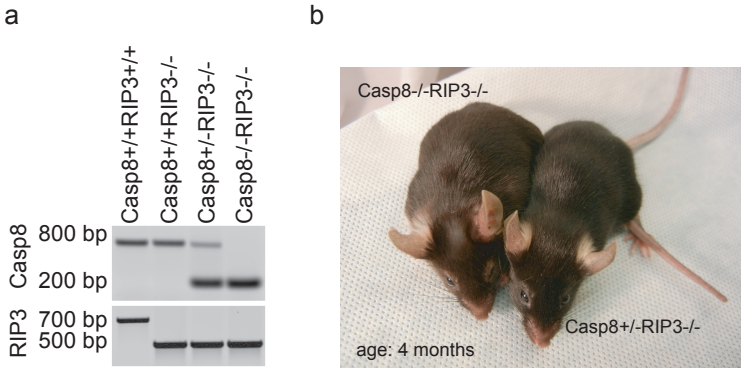


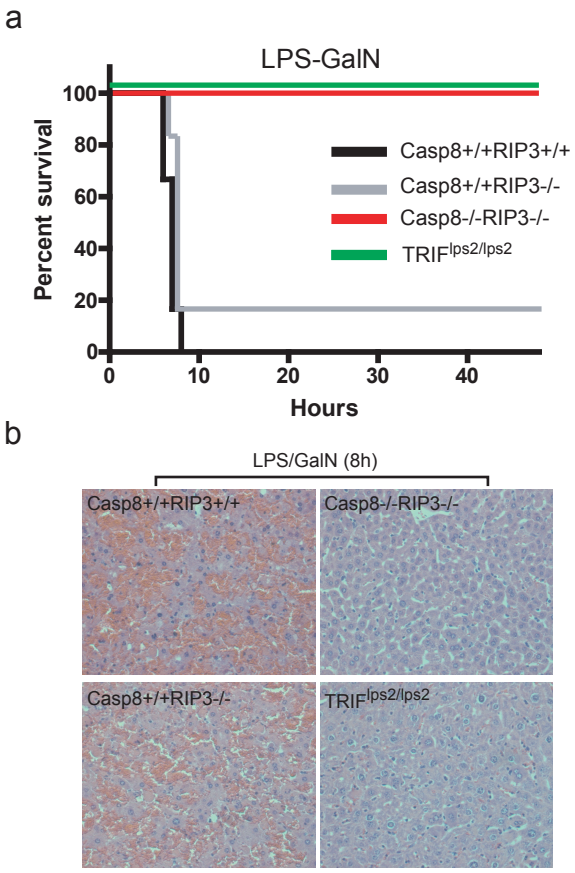
Supplementary Figure 1. Casp8 suppresses programmed necrosis. **(a)** Viability (left) and RIP3, RIP1, Casp8, and β-actin immunoblots (right) of L929 cells expressing a control scramble shRNA or RIP3-secific shRNA following transfection with non-targeting (NT) or Casp8-specific siRNA. Cell viability was determined 96 h post-transfection by measuring intracellular ATP levels (Cell Titer-Glo Luminescent Cell Viability Assay kit, Promega). **(b)** Viability (left) and M45 immunoblot (right) of L929 cells transduced with empty vector (EV), M45-myc, or M45*mut*RHIM-myc at 96 h post-transfection with NT or Casp8 siRNA. **(c)** Viability of L929 cells expressing a control scramble shRNA or RIP3-specific shRNA following treatment for 18 h with zVAD-fmk (25 μM) in the absence or presence of the RIP1 kinase inhibitor Nec-1 (30 μM). **(d)** Viability of L929 cells transduced with empty vector (EV), M45-myc, or M45*mut*RHIM-myc following treatment as described in c. **(e)** Percent cell death, calculated as the difference between the indicated treatment and the EV-transfected cell viability, in L929 cells expressing an EV or M45-myc (left), or control scramble shRNA or RIP3-specific shRNA (right), constructs at 96 h post-transfection with plasmid encoding M36 and cultured in the presence of Nec-1 (30μM) or vehicle DMSO for 12 h. **(f)** L929 cells carrying a control scramble shRNA or RIP3-specific shRNA following cotransfection with M36 or EV control plasmids together with a GFP expression plasmid. The percent GFP positive cells was calculated by comparing to control EV-transfected cells determined by flow cytometry at 48 h post-transfection.



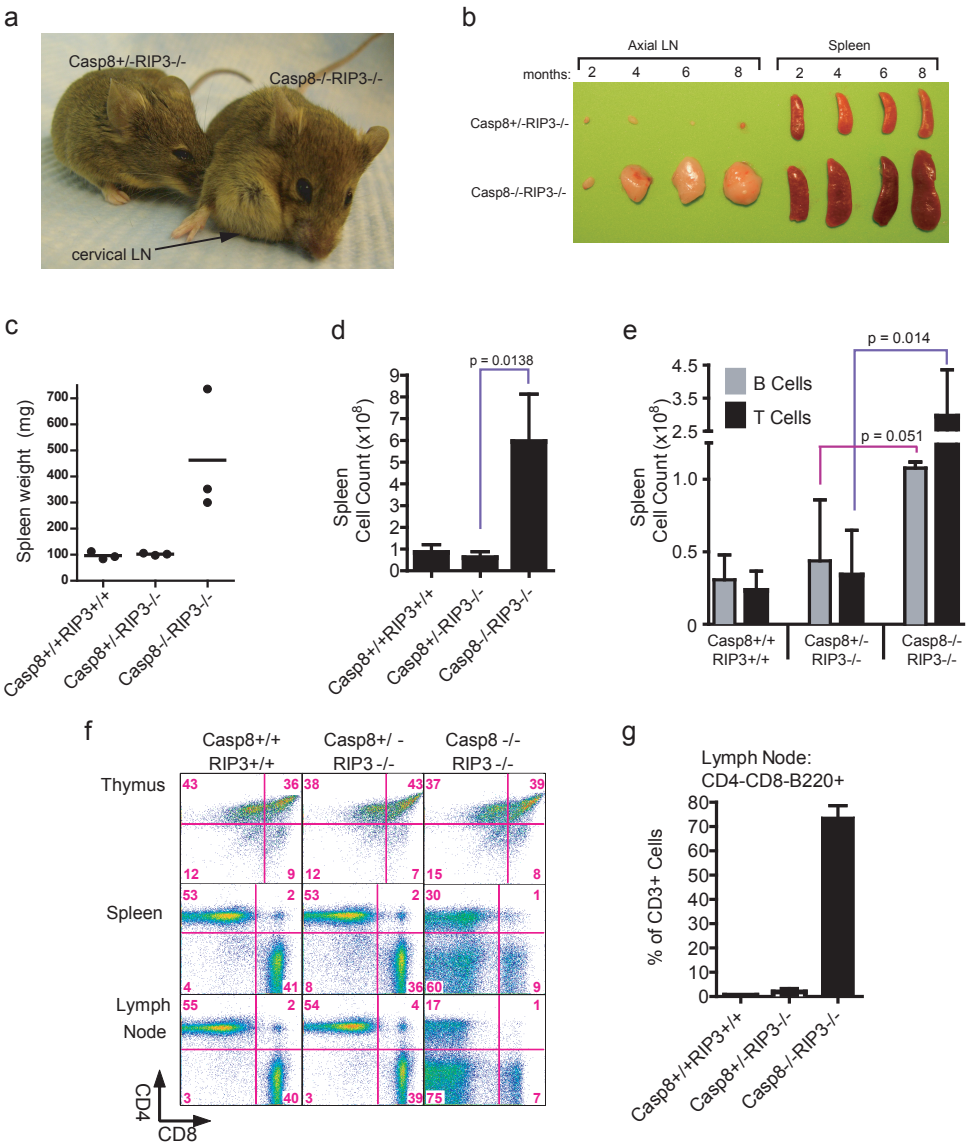
Supplementary Figure 2. Embryonic lethality and RIP3 detection in Casp8-deficient mice. **(a)** Photomicrographs of E11.5 yolk sac and embryo with the indicated genotype, highlighting the region of hyperemia (arrow in right panel). **(b)** PECAM (red), RIP3 (green) and DAPI (blue) fluorescent staining of representative *Casp8*$^{+/-}$*Rip3*$^{+/-}$ and *Casp8*$^{-/-}$*Rip3*$^{+/-}$ E10.5 yolk sacs (400X original magnification). **(c)** RIP3 (red), CD41 (green) and DAPI (blue) fluorescent staining of representative *Casp8*$^{+/-}$*Rip3*$^{+/-}$ yolk sacs (630X original magnification). **(d)** PECAM-1 (CD31) staining of a whole-mount E9.5 and E11.5 yolk sac from a representative *Casp8*$^{-/-}$*Rip3*$^{+/-}$ (left panels) and *Casp8*$^{-/-}$*Rip3*$^{-/-}$ (right panels) embryo (200X).



Supplementary Figure 3. *Casp8*$^{-/-}$*Rip3*$^{-/-}$ mice are viable. **(a)** PCR confirmation of genotype on tail DNA from the indicated *Casp8*$^{+/-}$*Rip3*$^{+/-}$ intercross progeny to detect wild-type (upper bands) and mutant (lower bands) *Casp8* and *Rip3* alleles. **(b)** Photograph of 4-month-old *Casp8*$^{-/-}$*Rip3*$^{-/-}$ mouse bred from a DKO cross along side a *Casp8*$^{+/-}$*Rip3*$^{-/-}$ mice bred from an intercross.



Supplementary Figure 4. Susceptibility to LPS+GalN induced hepatitis in *Casp8*$^{+/+}$*Rip3*$^{+/+}$, *Casp8*$^{+/+}$*Rip3*$^{-/-}$, *Casp8*$^{-/-}$*Rip3*$^{-/-}$ and control TRIF-deficient (*lps2*/*lps2*) mice. **(a)** Kaplan-Meier survival plot of indicated strains of mice following intraperitoneal inoculation with LPS (100 ng) and GalN (20 mg). **(b)** Histology of liver sections from indicated strains of mice 8h following injection with LPS/GalN.



Supplementary Figure 5. DKO mice accumulate aberrant T-cells. **(a)** Photographs of six-month-old *Casp8*$^{+/-}$*Rip3*$^{-/-}$ and *Casp8*$^{-/-}$*Rip3*$^{-/-}$ mice. The arrow indicates enlarged cervical LN present in the DKO mouse. **(b)** Images of spleen and axial LNs from *Casp8*$^{+/-}$*Rip3*$^{-/-}$ and *Casp8*$^{-/-}$ *Rip3*$^{-/-}$ mice of the indicated ages. **(c)** Graph of weights of spleen from mice of the indicated genotype. **(d)** The numbers of cells and **(e)** numbers of B and T cells recovered from spleens from mice with the indicated genotype. Samples were analyzed using Student's t-test. **(f)** CD4 vs. CD8 expression of CD3^{+} T cells in spleen (top panels), LN (middle panels) and thymus (bottom panels) identified as in C, in representative wild-type (left panels), *Casp8*$^{+/-}$*RIP3*$^{-/-}$ (middle panels) and *Casp8*$^{-/-}$*RIP3*$^{-/-}$ (right panels) mice. **(g)** Frequency (graph) and level of CD3^{+}CD4^{-}CD8^{-}B220^{+} T cells from LN of mice**.**